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10/16/01
§32

Patent
Attorney's Docket No. 002010-593

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
)
Jing WU et al.) Group Art Unit: Unassigned
)
Application No.: Unassigned) Examiner: Unassigned
(Div. of 08/996,422))
Filed: Herewith)
)
For: CYCLOALKYL, LACTAM,)
LACTONE AND RELATED)
COMPOUNDS, PHARMACEUTICAL)
COMPOSITIONS COMPRISING)
SAME, AND METHOD FOR)
INHIBITING β -AMYLOID PEPTIDE)
RELEASE AND/OR ITS SYNTHESIS)
BY USE OF SUCH COMPOUNDS)

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination on the merits and calculation of fees, please amend the above-identified application as follows:

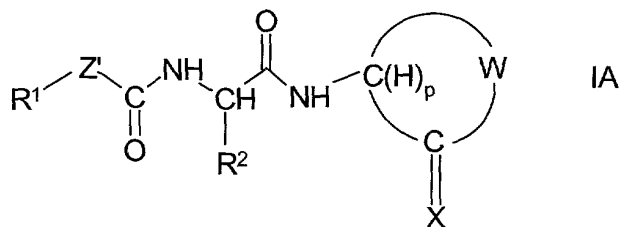
IN THE SPECIFICATION:

Please replace the first paragraph of page 1, appearing under the "Cross-Reference to Related Applications" with the follow paragraph: ✓

-- This application is a division of U.S. Application Serial No. 08/996,422 filed December 22, 1997, which claims priority under 35 U.S.C. §119(e) from U.S. Provisional Application No. 60/064,851 which was converted pursuant to 37 C.F.R. §1.53(b)(2)(ii) from U.S. Patent Application No. 08/780,025 filed December 23, 1996. --

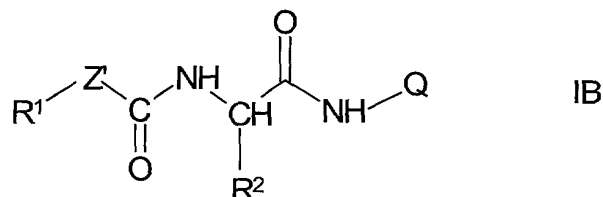
Please insert the following paragraphs between the third and fourth full paragraphs on page 14, line 27 insert: ✓

-- The compounds of formula I wherein m is 1 and n is 1 can be represented by the following formula:

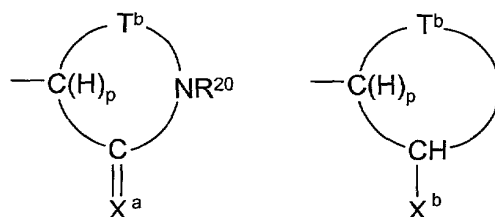


wherein R¹, R², W, X and p are as defined hereinabove with respect to formula I and Z' is represented by the formula -CX'X'', -T-CH₂- or -T-C(O)- where T is selected from the group consisting oxygen, sulfur, -NR⁵ where R⁵ is hydrogen, acyl, alkyl, aryl or heteroaryl group; X' is hydrogen, hydroxy or fluoro; X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group.

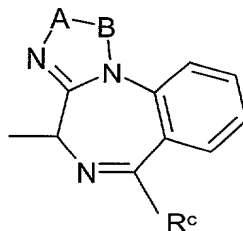
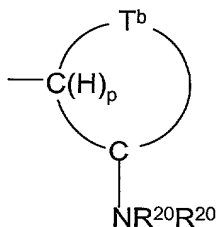
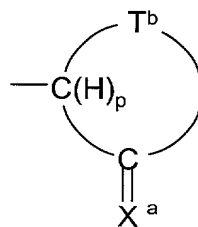
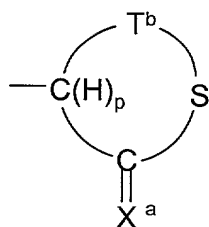
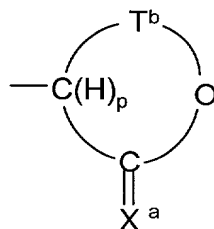
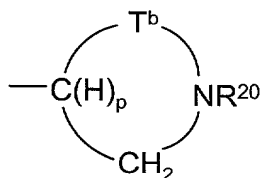
A further grouping of compounds within the invention can be represented by the following formula IB:



wherein R¹ and R² are defined hereinabove with respect to formula I, Z' is defined hereinabove with respect to formula IA, and Q is selected from the group of monocyclic and polycyclic groups having the formulas:



contd.
B 2



wherein T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, q is an integer of from 1 to 3;

X^a is oxo or thioxo; X^b is hydroxy ($-OH$) or mecapto ($-SH$);

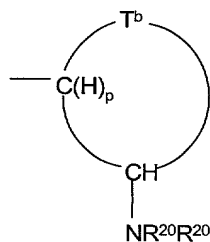
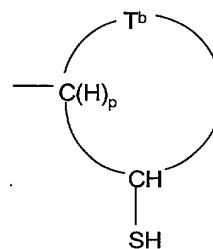
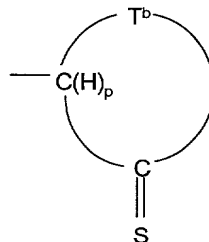
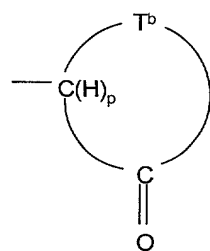
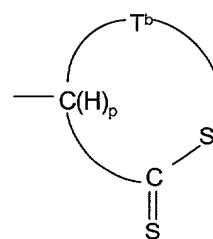
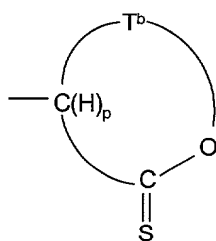
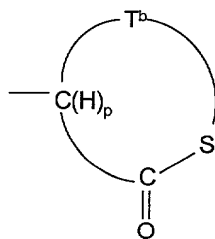
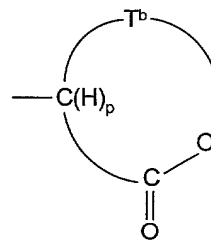
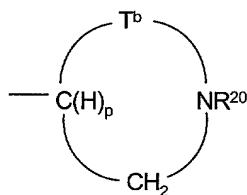
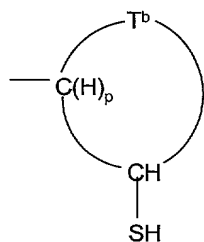
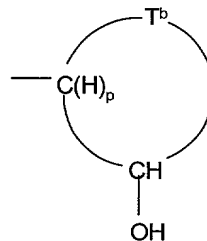
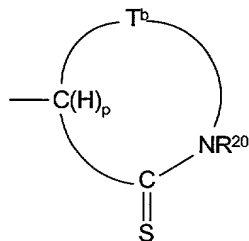
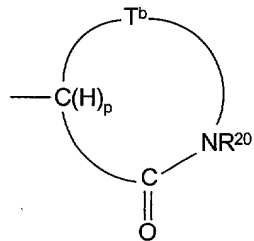
contd.
B 2 A-B is selected from the group consisting of alkylene, alkenylene, substituted alkylene, substituted alkenylene and $-N=CH-$; R^c is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, heteroaryl, heterocyclic, cycloalkyl, and substituted cycloalkyl; and

p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH.--

Please insert the following paragraphs before the first paragraph on page 87, line 1: ✓

-- The cyclic groups defined by W, together with $-C(H)_pC(=X)-$ includes the heterocyclic groups having the following formulas:

contd.
B³



cont'd
B3

wherein T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3;

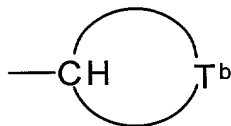
p is an integer equal to 0 or 1 such that when p is zero, the ring defined by W and $-C(H)_pC(=X)-$ is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH ;

and pharmaceutically acceptable salts thereof.--

On page 87 paragraph 1, (lines 1-21) please replace with the following: ✓

B4

-- Preferred cyclic groups defined by W and $-C(H)_pC(=X)-$ include cycloalkyl, lactone, lactam, benzazepinone, dibenzazepinone and benzodiazepine groups. In one preferred embodiment, the cyclic group defined by W and $-C(H)_pC(=X)-$, forms a cycloalkyl group of the formula:

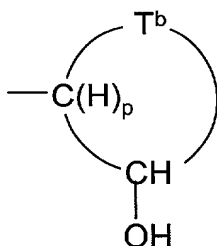


wherein T^b is selected from the group consisting of alkylene and substituted alkylene.--

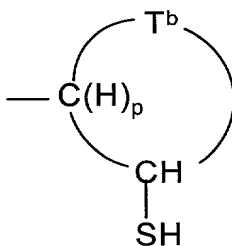
On page 88, second full paragraph (starting on line 8 through page 89, line 8) replace with:

-- In another preferred embodiment, the cyclic group defined by W , together with $-C(H)_pC(=X)-$ is a ring of the formula:

contd.
B4



or



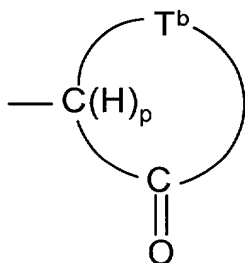
wherein p is zero or one, T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.--

On page 90, second full paragraph (starting at line 9 through page 91, line 10) replace with:

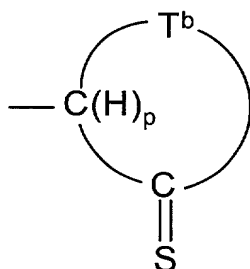
-- Yet another preferred embodiment of the cyclic group defined by W, together with $-C(H)_pC(=X)-$, is a ring of the formula:

B5

contd.
B5



or



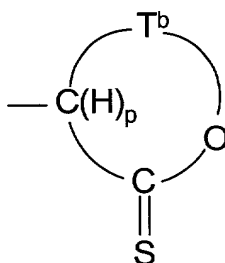
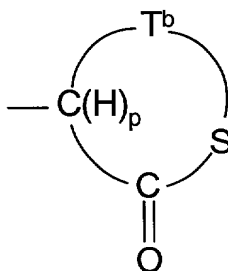
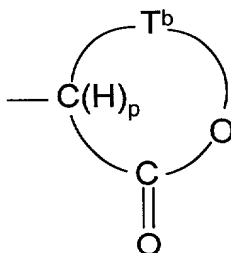
wherein p is zero or one, T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.--

On page 92, second full paragraph (starting at line 7 through page 93, line 37) replace with:

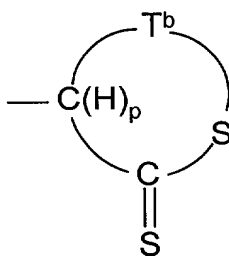
-- In another preferred embodiment, the cyclic group defined by W, together with $-C(H)_pC(=X)-$, forms a ring of the formula:

B6

contd
B6



or



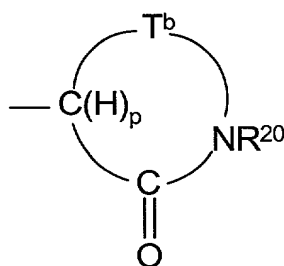
contd

B 6

wherein p is zero or one, T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.--

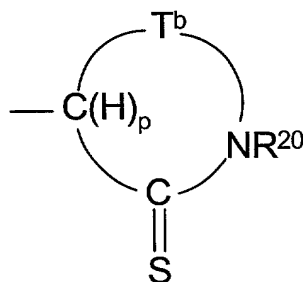
On page 94, second full paragraph (starting on line 20 through page 95, line 30) replace with: ✓

-- In another preferred embodiment, the cyclic group defined by W and $-C(H)_pC(=X)-$, forms a lactam ring of the formula:



or a thiolactam ring of the formula:

contd.
B 7

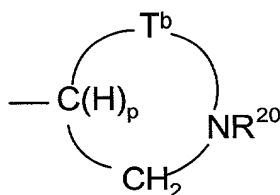


wherein p is zero or one, T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.--

On page 99, first paragraph (on lines 1-22) replace with: ✓

B 8

-- In another preferred embodiment, the cyclic group defined by W, together with $-C(H)_pC(=X)-$, forms a ring of the formula:

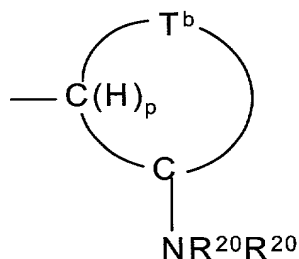


wherein p is zero or one, T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a

contd.
B8 substituent selected from the group consisting of -O-, -S- and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and q is an integer of from 1 to 3.--

On page 99, second full paragraph (starting at line 24 through page 100, line 10) replace with:

B^c -- A still further preferred embodiment is directed to a ring group defined by W, together with $-C(H)_pC(=X)-$, of the formula:

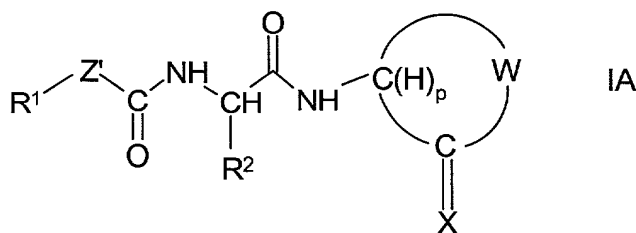


wherein p is zero or one, T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of -O-, -S- and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and q is an integer of from 1 to 3.--

IN THE CLAIMS:

Cancel Claims 1-90, without prejudice and add the following claims:

91. (New) A method for inhibiting β -amyloid peptide release and/or its synthesis in a cell which method comprises administering to such a cell an amount of a compound or a mixture of compounds effective in inhibiting the cellular release and/or synthesis of β -amyloid peptide wherein said compounds are represented by formula IA:



wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic;

Z' is represented by the formula $-CX'X''-$, $-T-CH_2-$ or $-T-C(O)-$ where T is selected from the group consisting oxygen, sulfur, $-NR^5$ where R^5 is hydrogen, acyl, alkyl, optionally substituted aryl or optionally substituted heteroaryl group; X' is hydrogen, hydroxy or fluoro; X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

R^2 is selected from the group consisting of alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, 2-aminopyrid-6-yl, 2-methylcyclopentyl, cyclohex-2-enyl and $-(CH_2)_4NHC(O)OC(CH_3)_3$;

W , together with $-C(H)_pC(=X)-$, forms a cycloalkyl, cycloalkenyl, optionally substituted heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, optionally substituted heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system with one or more ring structures selected from the group consisting of

contd.
B10

cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, -NHC(O)R⁴, -NH₂SO₂R⁴, -C(O)NH₂, -C(O)NHR⁴, -C(O)NR⁴R⁴, -S(O)R⁴, -S(O)₂R⁴, -S(O)₂NHR⁴ and -S(O)₂NR⁴R⁴ where each R⁴ is independently selected from the group consisting of alkyl, substituted alkyl, or optionally substituted aryl;

X is selected from the group consisting of =O; =S; -H, -OH; H, -SH; and H, H;

p is an integer equal to 0 or 1 such that when p is zero, the ring defined by W and -C(H)_pC(=X)- is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

and pharmaceutically acceptable salts thereof;

with the following provisos:

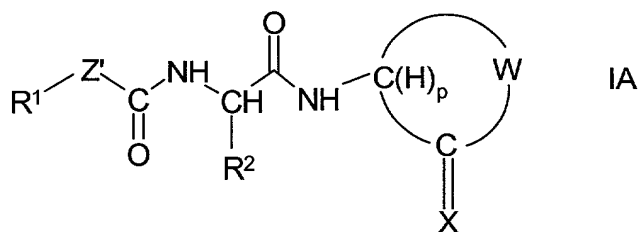
- A. when R¹ is 3,5-difluorophenyl, R² is -CH₃, Z' is -CH₂-, and p is 1, then W, together with >CH and >C=X, does not form a 2-(S)-indanol group;
- B. when R¹ is phenyl, R² is -CH₃, Z' is -CH₂-, p is 1, then W, together with >CH and >C=X, does not form a trans-2-hydroxy-cyclohex-1-yl group;
- C. when R¹ is cyclopropyl, R² is -CH₃, Z' is -CH₂-, and p is 1, then W, together with >CH and >C=X, does not form an N-methylcaprolactam group;
- D. when R¹ is 4-chlorobenzoyl-CH₂-, R² is -CH₃, Z' is -CH₂-, and p is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;
- E. when R¹ is 2-phenylphenyl, R² is -CH₃, Z' is -CH₂-, and p is 1, then W, together with >CH and >C=X, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;
- F. when R¹ is CH₃OC(O)CH₂-, R² is -CH₃, Z' is -CH₂-, and p is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-(t-butylC(O)CH₂)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

contd.
B¹⁰
G. when R¹ is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, CH₃OC(O)CH₂-, 4-HOCH₂-phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl, or CH₃S-, R² is -CH₃, Z' is -CH₂-, and p is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH₂CH₂-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

H. when R¹ is 2,6-difluorophenyl, R² is -CH₃, Z' is -CH(OH)-, and p is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH₂CH₂-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

I. when the ring defined by W and -C(H)_pC(=X)- forms a cycloalkyl, then it does not form a cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

92. (New) A method for preventing the onset of AD in a human patient at risk for developing AD which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula IA:



wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic;

Z' is represented by the formula -CX'X''-, -T-CH₂- or -T-C(O)- where T is selected from the group consisting oxygen, sulfur, -NR⁵ where R⁵ is hydrogen, acyl, alkyl, optionally substituted aryl or optionally substituted heteroaryl group; X' is hydrogen, hydroxy or fluoro; X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

contd.
B 10

R^2 is selected from the group consisting of alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, 2-aminopyrid-6-yl, 2-methylcyclopentyl, cyclohex-2-enyl and $-(CH_2)_4NHC(O)OC(CH_3)_3$;

W, together with $-C(H)_pC(=X)-$, forms a cycloalkyl, cycloalkenyl, optionally substituted heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, optionally substituted heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, $-NHC(O)R^4$, $-NHSO_2R^4$, $-C(O)NH_2$, $-C(O)NHR^4$, $-C(O)NR^4R^4$, $-S(O)R^4$, $-S(O)_2R^4$, $-S(O)_2NHR^4$ and $-S(O)_2NR^4R^4$ where each R^4 is independently selected from the group consisting of alkyl, substituted alkyl, or optionally substituted aryl;

X is selected from the group consisting of $=O$; $=S$; $-H$, $-OH$; H , $-SH$; and H , H ;

p is an integer equal to 0 or 1 such that when p is zero, the ring defined by W and $-C(H)_pC(=X)-$ is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

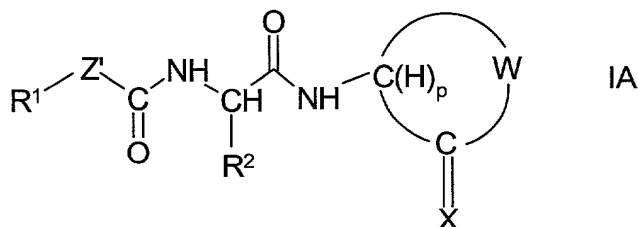
and pharmaceutically acceptable salts thereof;

with the following provisos:

- A. when R^1 is 3,5-difluorophenyl, R^2 is $-CH_3$, Z' is $-CH_2-$, and p is 1, then W, together with $>CH$ and $>C=X$, does not form a 2-(S)-indanol group;
- B. when R^1 is phenyl, R^2 is $-CH_3$, Z' is $-CH_2-$, p is 1, then W, together with $>CH$ and $>C=X$, does not form a trans-2-hydroxy-cyclohex-1-yl group;
- C. when R^1 is cyclopropyl, R^2 is $-CH_3$, Z' is $-CH_2-$, and p is 1, then W, together with $>CH$ and $>C=X$, does not form an N-methylcaprolactam group;

I. when the ring defined by W and -C(H)_pC(=X)- forms a cycloalkyl, then it does not form a cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

93. (New) A method for treating a human patient with AD in order to inhibit further deterioration in the condition of that patient which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula IA:



contd.
B¹⁰

wherein R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic;

Z' is represented by the formula -CX'X"-, -T-CH₂- or -T-C(O)- where T is selected from the group consisting oxygen, sulfur, -NR⁵ where R⁵ is hydrogen, acyl, alkyl, optionally substituted aryl or optionally substituted heteroaryl group; X' is hydrogen, hydroxy or fluoro; X" is hydrogen, hydroxy or fluoro, or X' and X" together form an oxo group;

R² is selected from the group consisting of alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, 2-aminopyrid-6-yl, 2-methylcyclopentyl, cyclohex-2-enyl and -(CH₂)₄NHC(O)OC(CH₃)₃;

W, together with -C(H)_pC(=X)-, forms a cycloalkyl, cycloalkenyl, optionally substituted heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, optionally substituted heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, -NHC(O)R⁴, -NHSO₂R⁴, -C(O)NH₂, -C(O)NHR⁴, -C(O)NR⁴R⁴, -S(O)R⁴, -S(O)₂R⁴, -S(O)₂NHR⁴ and -S(O)₂NR⁴R⁴ where each R⁴ is independently selected from the group consisting of alkyl, substituted alkyl, or optionally substituted aryl;

X is selected from the group consisting of =O; =S; -H, -OH; H, -SH; and H, H;

p is an integer equal to 0 or 1 such that when p is zero, the ring defined by W and

contd.
B10
-C(H)_pC(=X)- is unsaturated at the carbon atom of ring attachment to NH and when *p* is one, the ring is saturated at the carbon atom of ring attachment to NH;

and pharmaceutically acceptable salts thereof;

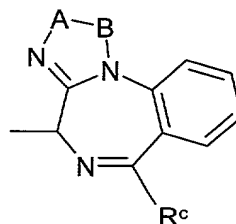
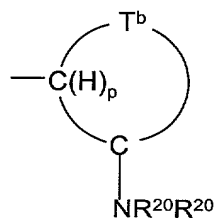
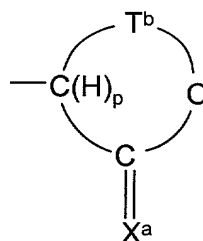
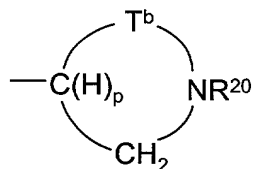
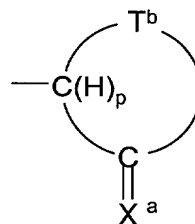
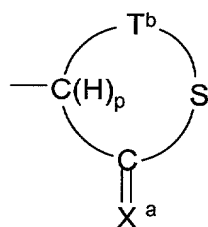
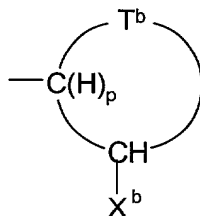
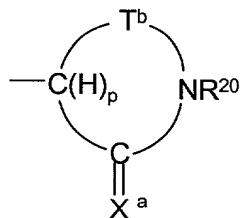
with the following provisos:

- A. when R¹ is 3,5-difluorophenyl, R² is -CH₃, Z' is -CH₂-, and *p* is 1, then W, together with >CH and >C=X, does not form a 2-(S)-indanol group;
- B. when R¹ is phenyl, R² is -CH₃, Z' is -CH₂-, *p* is 1, then W, together with >CH and >C=X, does not form a trans-2-hydroxy-cyclohex-1-yl group;
- C. when R¹ is cyclopropyl, R² is -CH₃, Z' is -CH₂-, and *p* is 1, then W, together with >CH and >C=X, does not form an N-methylcaprolactam group;
- D. when R¹ is 4-chlorobenzoyl-CH₂-, R² is -CH₃, Z' is -CH₂-, and *p* is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;
- E. when R¹ is 2-phenylphenyl, R² is -CH₃, Z' is -CH₂-, and *p* is 1, then W, together with >CH and >C=X, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;
- F. when R¹ is CH₃OC(O)CH₂-, R² is -CH₃, Z' is -CH₂-, and *p* is 1, then W, together with >CH and >C=X, does not form an 2,3-dihydro-1-(*t*-butylC(O)CH₂-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;
- G. when R¹ is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, CH₃OC(O)CH₂-, 4-HOCH₂-phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl, or CH₃S-, R² is -CH₃, Z' is -CH₂-, and *p* is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH₂CH₂-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;
- H. when R¹ is 2,6-difluorophenyl, R² is -CH₃, Z' is -CH(OH)-, and *p* is 1, then W, together with >CH and >C=X, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH₂CH₂-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;
- I. when the ring defined by W and -C(H)_pC(=X)- forms a cycloalkyl, then it does not form a cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

[illegible]
$$\begin{array}{c} \text{R}^1-\text{Z}'-\text{C}(=\text{O})-\text{NH}-\text{CH}(\text{R}^2)-\text{C}(=\text{O})-\text{NH}-\text{Q} \end{array} \quad \text{IB}$$

Q is selected from the group of monocyclic and fused polycyclic groups having the formulas:

contd.
B 10



wherein T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently

control.
B10
selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, q is an integer of from 1 to 3;

X^a is oxo or thioxo; X^b is -OH or -SH;

A-B is selected from a group of alkylene, alkenylene, substituted alkylene, substituted alkenylene and -N=CH-; R^c is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, cycloalkyl, and substituted cycloalkyl;

p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

and pharmaceutically acceptable salts thereof;

with the following provisos:

- A. when R^1 is 3,5-difluorophenyl, R^2 is -CH₃, Z' is -CH₂-, and p is 1, then the group defined by Q, does not form a 2-(S)-indanol group;
- B. when R^1 is phenyl, R^2 is -CH₃, Z' is -CH₂-, and p is 1, then the group defined by Q, does not form a trans-2-hydroxy-cyclohex-1-yl group;
- C. when R^1 is cyclopropyl, R^2 is -CH₃, Z' is -CH₂-, and p is 1, then the group defined by Q, does not form an N-methylcaprolactam group;
- D. when R^1 is 4-chlorobenzoyl-CH₂-, R^2 is -CH₃, Z' is -CH₂-, and p is 1, then the group defined by Q, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;
- E. when R^1 is 2-phenylphenyl, R^2 is -CH₃, Z' is -CH₂-, and p is 1, then the group defined by Q, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;

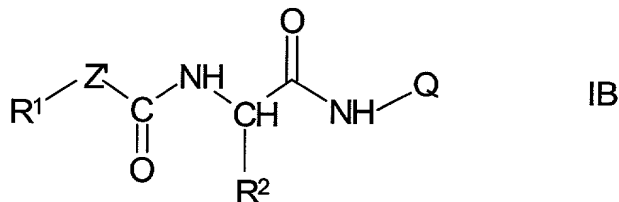
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B10
F. when R^1 is $\text{CH}_3\text{OC(O)CH}_2-$, R^2 is $-\text{CH}_3$, Z' is $-\text{CH}_2-$, and p is 1, then the group defined by Q, does not form an 2,3-dihydro-1-(*t*-butylC(O)CH₂-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

G. when R^1 is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, $\text{CH}_3\text{OC(O)CH}_2-$, 4-HOCH₂-phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl, or $\text{CH}_3\text{S}-$, R^2 is $-\text{CH}_3$, Z' is $-\text{CH}_2-$, and p is 1, then the group defined by Q, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH₂CH₂-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

H. when R^1 is 2,6-difluorophenyl, R^2 is $-\text{CH}_3$, Z' is $-\text{CH(OH)-}$, and p is 1, then the group defined by Q, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH₂CH₂-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

I. when the ring defined by Q forms a cycloalkyl, then it does not form a cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

96. (New) A method for preventing the onset of AD in a human patient at risk for developing AD which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula IB:



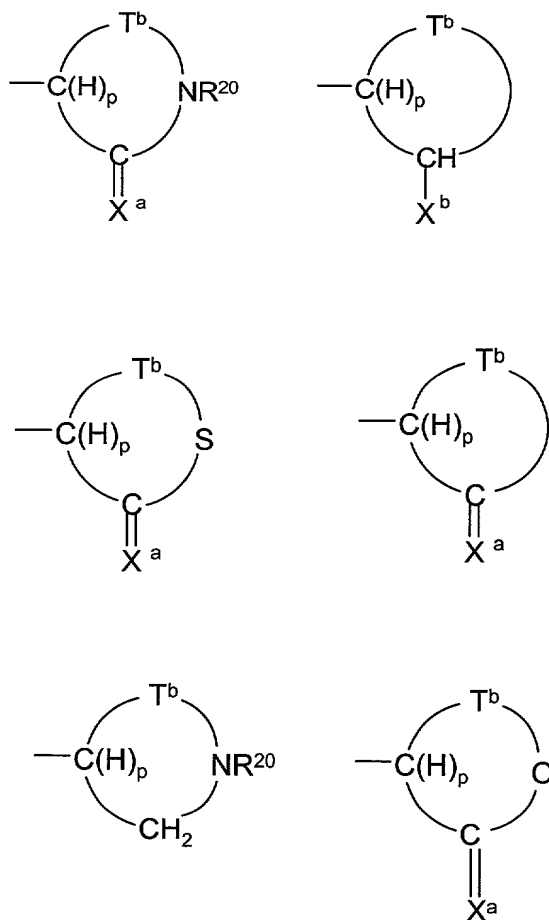
wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic;

Z' is represented by the formula $-\text{CX}'\text{X}''-$, $-\text{T-CH}_2-$ or $-\text{T-C(O)-}$ where T is selected from the group consisting oxygen, sulfur, $-\text{NR}^5$ where R^5 is hydrogen, acyl, alkyl, optionally

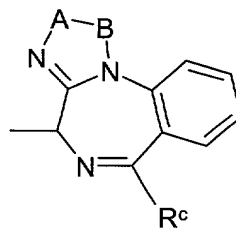
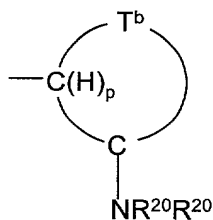
contol.
B¹⁰
substituted aryl or optionally substituted heteroaryl group; X' is hydrogen, hydroxy or fluoro;
X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

R² is selected from the group consisting of alkyl, alkenyl, alkynyl, substituted alkyl,
substituted alkenyl, substituted alkynyl, cycloalkyl, optionally substituted aryl, optionally
substituted heteroaryl, optionally substituted heterocyclic, 2-aminopyrid-6-yl,
2-methylcyclopentyl, cyclohex-2-enyl and -(CH₂)₄NHC(O)OC(CH₃)₃;

Q is selected from the group of monocyclic and fused polycyclic groups having the
formulas:



contd.
B¹⁰



wherein T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, q is an integer of from 1 to 3;

X^a is oxo or thioxo; X^b is $-OH$ or $-SH$;

$A-B$ is selected from a group of alkylene, alkenylene, substituted alkylene, substituted alkenylene and $-N=CH-$; R^c is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, cycloalkyl, and substituted cycloalkyl;

p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH ;

and pharmaceutically acceptable salts thereof;

with the following provisos:

A. when R^1 is 3,5-difluorophenyl, R^2 is $-CH_3$, Z' is $-CH_2-$, and p is 1, then the group defined by Q , does not form a 2-(S)-indanol group;

contd.
B¹⁰
B. when R¹ is phenyl, R² is -CH₃, Z' is -CH₂-, and *p* is 1, then the group defined by Q, does not form a trans-2-hydroxy-cyclohex-1-yl group;

C. when R¹ is cyclopropyl, R² is -CH₃, Z' is -CH₂-, and *p* is 1, then the group defined by Q, does not form an N-methylcaprolactam group;

D. when R¹ is 4-chlorobenzoyl-CH₂-, R² is -CH₃, Z' is -CH₂-, and *p* is 1, then the group defined by Q, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;

E. when R¹ is 2-phenylphenyl, R² is -CH₃, Z' is -CH₂-, and *p* is 1, then the group defined by Q, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;

F. when R¹ is CH₃OC(O)CH₂-, R² is -CH₃, Z' is -CH₂-, and *p* is 1, then the group defined by Q, does not form an 2,3-dihydro-1-(*t*-butylC(O)CH₂)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

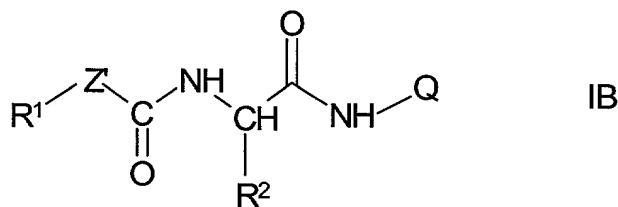
G. when R¹ is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, CH₃OC(O)CH₂-, 4-HOCH₂-phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl, or CH₃S-, R² is -CH₃, Z' is -CH₂-, and *p* is 1, then the group defined by Q, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH₂CH₂)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

H. when R¹ is 2,6-difluorophenyl, R² is -CH₃, Z' is -CH(OH)-, and *p* is 1, then the group defined by Q, does not form a 2,3-dihydro-1-(N,N-diethylamino-CH₂CH₂)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

I. when the ring defined by Q forms a cycloalkyl, then it does not form a cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

97. (New) A method for treating a human patient with AD in order to inhibit further deterioration in the condition of that patient which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula IB:

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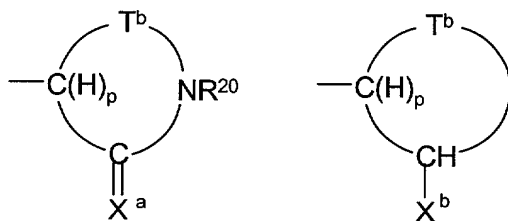


wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic;

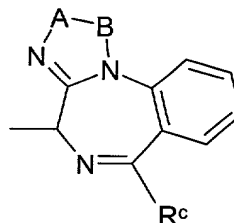
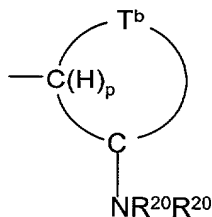
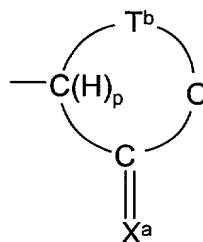
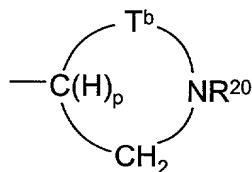
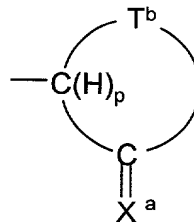
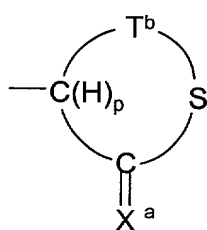
Z' is represented by the formula $-\text{CX}'\text{X}''-$, $-\text{T}-\text{CH}_2-$ or $-\text{T}-\text{C}(\text{O})-$ where T is selected from the group consisting oxygen, sulfur, $-\text{NR}^5$ where R^5 is hydrogen, acyl, alkyl, optionally substituted aryl or optionally substituted heteroaryl group; X' is hydrogen, hydroxy or fluoro; X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

R^2 is selected from the group consisting of alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, 2-aminopyrid-6-yl, 2-methylcyclopentyl, cyclohex-2-enyl and $-(\text{CH}_2)_4\text{NHC}(\text{O})\text{OC}(\text{CH}_3)_3$;

Q is selected from the group of monocyclic and fused polycyclic groups having the formulas:



contd.
B¹⁰



wherein T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, -(R²¹Z^a)_qR²¹- and -Z^aR²¹- where Z^a is a substituent selected from the group consisting of -O-, -S- and >NR²⁰, each R²⁰ is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R²¹ is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is -O- or -S-, any

contd.
B10
unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, q is an integer of from 1 to 3;

X^a is oxo or thioxo; X^b is -OH or -SH;

A-B is selected from a group of alkylene, alkenylene, substituted alkylene, substituted alkenylene and -N=CH-; R^c is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, cycloalkyl, and substituted cycloalkyl;

p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

and pharmaceutically acceptable salts thereof;

with the following provisos:

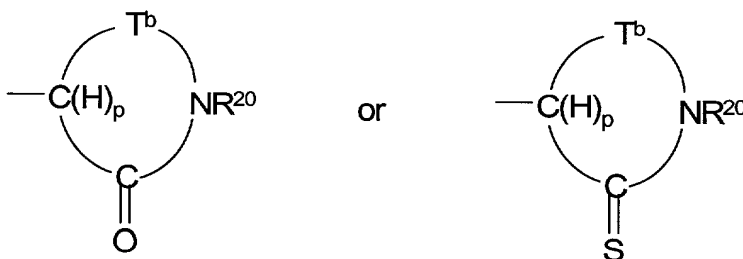
- A. when R^1 is 3,5-difluorophenyl, R^2 is -CH₃, Z' is -CH₂-, and p is 1, then the group defined by Q, does not form a 2-(S)-indanol group;
- B. when R^1 is phenyl, R^2 is -CH₃, Z' is -CH₂-, and p is 1, then the group defined by Q, does not form a trans-2-hydroxy-cyclohex-1-yl group;
- C. when R^1 is cyclopropyl, R^2 is -CH₃, Z' is -CH₂-, and p is 1, then the group defined by Q, does not form an N-methylcaprolactam group;
- D. when R^1 is 4-chlorobenzoyl-CH₂-, R^2 is -CH₃, Z' is -CH₂-, and p is 1, then the group defined by Q, does not form an 2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one;
- E. when R^1 is 2-phenylphenyl, R^2 is -CH₃, Z' is -CH₂-, and p is 1, then the group defined by Q, does not form an 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one;
- F. when R^1 is CH₃OC(O)CH₂-, R^2 is -CH₃, Z' is -CH₂-, and p is 1, then the group defined by Q, does not form an 2,3-dihydro-1-(*t*-butylC(O)CH₂-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;
- G. when R^1 is 4-ethoxyphenyl, 2,4,6-trimethylphenyl, 4-phenylphenyl, CH₃OC(O)CH₂-, 4-HOCH₂-phenyl, 2,4,6-trifluorophenyl, 2-trifluoromethyl-4-fluorophenyl,

or $\text{CH}_3\text{S}-$, R^2 is $-\text{CH}_3$, Z' is $-\text{CH}_2-$, and p is 1, then the group defined by Q, does not form a 2,3-dihydro-1-(N,N-diethylamino- CH_2CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

H. when R^1 is 2,6-difluorophenyl, R^2 is $-\text{CH}_3$, Z' is $-\text{CH}(\text{OH})-$, and p is 1, then the group defined by Q, does not form a 2,3-dihydro-1-(N,N-diethylamino- CH_2CH_2-)-5-(2-pyridyl)-1H-1,4-benzodiazepin-2-one;

I. when the ring defined by Q forms a cycloalkyl, then it does not form a cycloalkyl of from 3 to 8 carbon atoms optionally substituted with 1 to 3 alkyl groups.

98. (New) The method according to Claims 95, 96 or 97 wherein Q is a lactam or thiolactam ring of the formula:

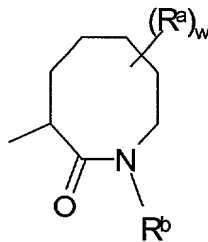
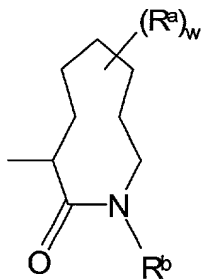
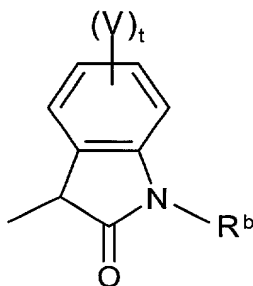
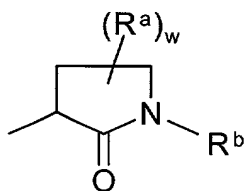


wherein p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

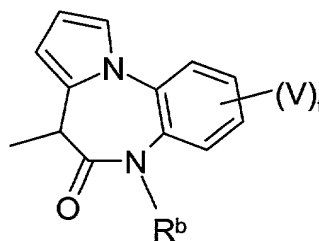
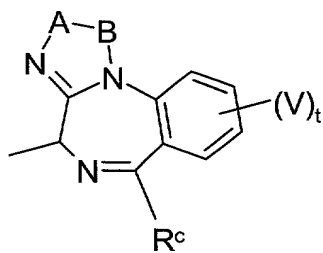
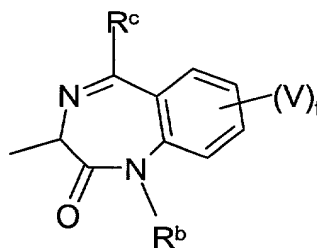
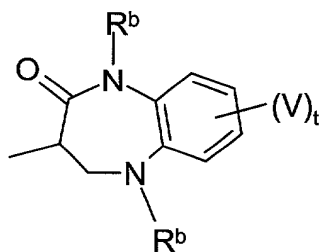
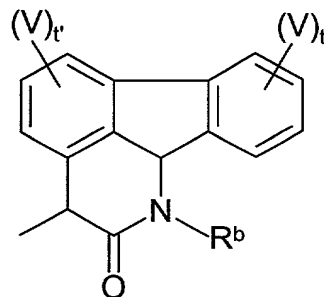
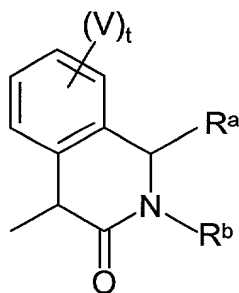
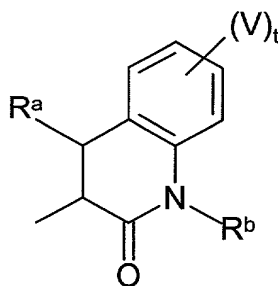
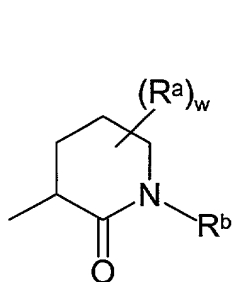
T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(\text{R}^{21}\text{Z}^a)_q\text{R}^{21}-$ and $-\text{Z}^a\text{R}^{21}-$ where Z^a is a substituent selected from the group consisting of $-\text{O}-$, $-\text{S}-$ and $>\text{NR}^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-\text{O}-$ or $-\text{S}-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-\text{O}-$ or $-\text{S}-$, and q is an integer of from 1 to 3.

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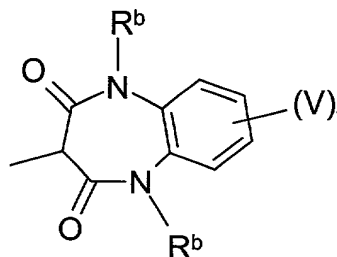
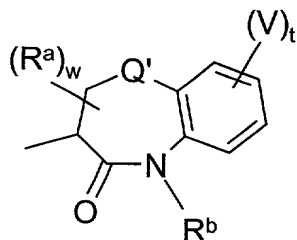
99. (New) The method according to Claims 95, 96 or 97 wherein Q is selected from the group having the formula:



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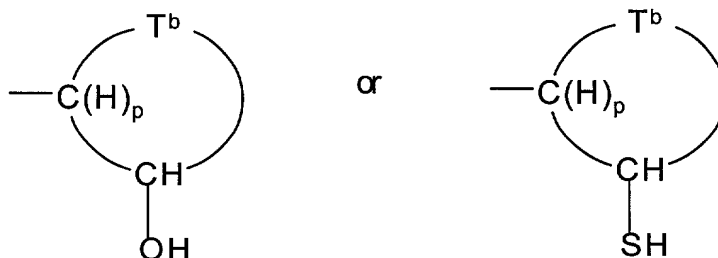
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wherein A-B is selected from the group consisting of alkylene, alkenylene, substituted alkylene, substituted alkenylene and -N=CH-; Q' is oxygen or sulfur; each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, optionally substituted alkaryl, optionally substituted aryl, optionally substituted aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, optionally substituted heteroaryl, thioalkoxy, substituted thioalkoxy and trihalomethyl; R^a is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, carboxyl, carboxyl alkyl, cyano and halo; R^b is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic; R^c is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, cycloalkyl, and substituted cycloalkyl; *t* is an integer from 0 to 4; *t*' is an integer from 0 to 3; and *w* is an integer from 0 to 3.

100. (New) The method according to Claims 95, 96 or 97 wherein Q is a monocyclic or fused polycyclic ring having the formula:

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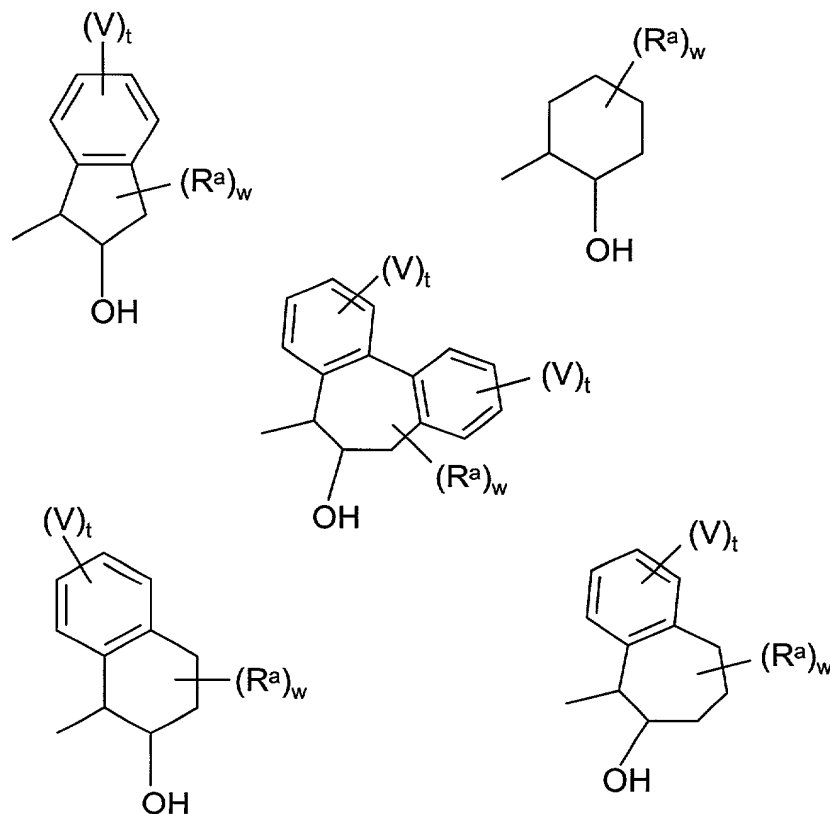


wherein p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

101. (New) The method according to Claim 100 wherein Q is selected from the group consisting of:

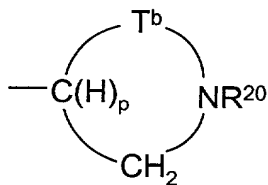
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wherein each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, optionally substituted alkaryl, optionally substituted aryl, optionally substituted aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, optionally substituted heteroaryl, thioalkoxy, substituted thioalkoxy and trihalomethyl; R^a is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, carboxyl, carboxyl alkyl, cyano and halo; t is an integer from 0 to 4; and w is an integer from 0 to 3.

102. (New) The method according to Claims 95, 96 or 97 wherein Q is a group having the formula:

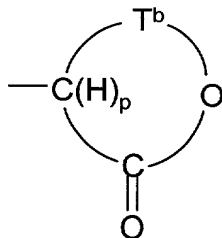
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wherein p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

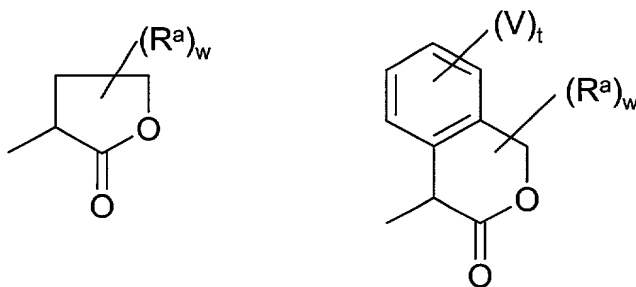
103. (New) The method according to Claims 95, 96 or 97 wherein Q is a group having the formula:



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wherein p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

104. (New) The method according to Claim 103 wherein Q is selected from the group having the formula:



wherein each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, optionally substituted alkaryl, optionally substituted aryl, optionally substituted aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, optionally substituted heteroaryl, thioalkoxy, substituted thioalkoxy and trihalomethyl;

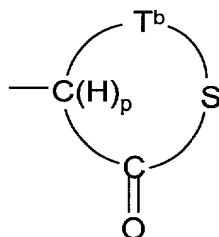
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R^a is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, carboxyl, carboxyl alkyl, cyano and halo;

t is an integer from 0 to 4; and

w is an integer from 0 to 3.

105. (New) The method according to Claims 95, 96 or 97 wherein Q is selected from the group having the formula:

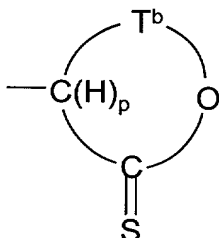


wherein p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

106. (New) The method according to Claims 95, 96 or 97 wherein Q has the formula:

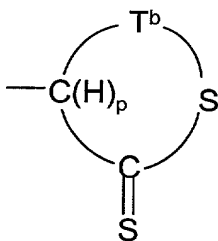
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wherein p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

107. (New) The method according to Claims 95, 96 or 97 wherein Q has the formula:

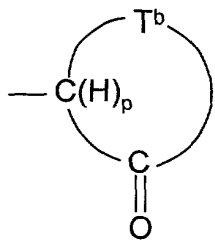


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wherein p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of -O-, -S- and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and q is an integer of from 1 to 3.

108. (New) The method according to Claims 95, 96 or 97 wherein Q has the formula:

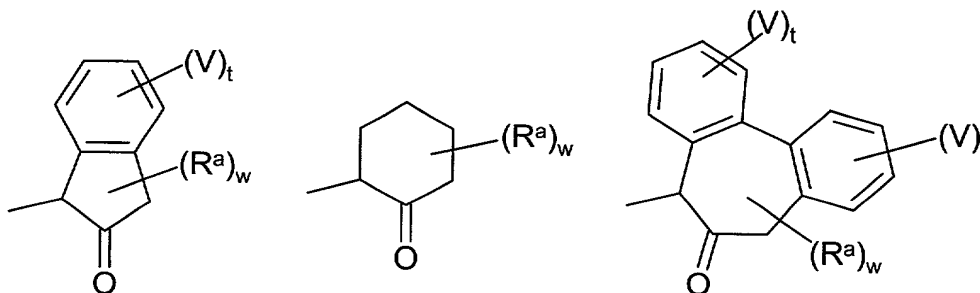


wherein p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of -O-, -S- and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl,

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B10 substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and q is an integer of from 1 to 3.

109. (New) The method according to Claim 108 wherein Q is selected from the group having the formula:



wherein each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, optionally substituted alkaryl, optionally substituted aryl, optionally substituted aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, optionally substituted heteroaryl, thioalkoxy, substituted thioalkoxy and trihalomethyl;

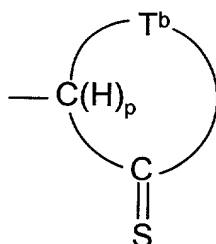
R^a is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, carboxyl, carboxyl alkyl, cyano and halo;

t is an integer from 0 to 4; and

w is an integer from 0 to 3.

110. (New) The method according to Claims 95, 96 or 97 wherein Q has the formula:

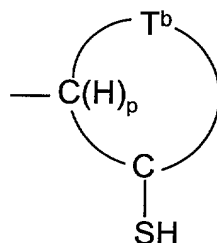
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wherein p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

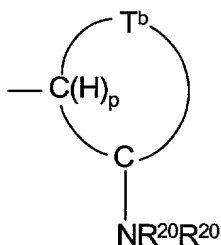
111. (New) The method according to Claims 95, 96 or 97 wherein Q has the formula:



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wherein p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

112. (New) The method according to Claims 95, 96 or 97 wherein Q has the formula:



wherein p is an integer equal to 0 or 1 such that when p is zero, the ring defined by Q is unsaturated at the carbon atom of ring attachment to NH and when p is one, the ring is saturated at the carbon atom of ring attachment to NH;

T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl,

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substituted alkyl, substituted alkenyl, substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z^a is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and q is an integer of from 1 to 3.

113. (New) The method according to any of Claims 91-93 or 95-97 wherein R^1 is selected from the group consisting of unsubstituted aryls and mono-, di- and tri-substituted phenyl groups.

114. (New) The method according to any of Claims 91-93 or 95-97 wherein R^1 is selected from the group consisting of:

phenyl, 1-naphthyl, 2-naphthyl, 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl, 2-methoxyphenyl, 2-phenoxyphenyl, 2-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl, 4-*iso*-propylphenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxymethylphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-nitrophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl, 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-di-trifluoromethylphenyl, 3,5-dimethoxyphenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-trifluorophenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri-(trifluoromethyl)phenyl, 2,4,6-trifluorophenyl, 2,4,6-trimethylphenyl, 2,4,6-tri-(trifluoromethyl)phenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-chlorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl,

contd.
B 10

4-phenylphenyl, 2-fluoro-3-trifluoromethylphenyl, adamantyl, benzyl, 2-phenylethyl, 3-phenyl-*n*-propyl, 4-phenyl-*n*-butyl, methyl, ethyl, *n*-propyl, *iso*-propyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-valeryl, *n*-hexyl, cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopent-1-enyl, cyclopent-2-enyl, cyclohex-1-enyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclohexyl, -CH₂-cyclopentyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclobutyl, -CH₂CH₂-cyclohexyl, -CH₂CH₂-cyclopentyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, fluoropyridyls, chloropyridyls, thien-2-yl, thien-3-yl, benzothiazol-4-yl, 2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl, thionaphthen-3-yl, thionaphthen-4-yl, 2-chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thien-5-yl, 6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, 2-phenyloxazol-4-yl, indol-3-yl, 1-phenyl-tetraol-5-yl, allyl, 2-(cyclohexyl)ethyl, (CH₃)₂C=CCH₂CH₂CH(CH₃)-, ϕ C(O)CH₂-, thien-2-yl-methyl, 2-(thien-2-yl)ethyl, 3-(thien-2-yl)-*n*-propyl, 2-(4-nitrophenyl)ethyl, 2-(4-methoxyphenyl)ethyl, norboran-2-yl, (4-methoxyphenyl)methyl, (2-methoxyphenyl)methyl, (3-methoxyphenyl)methyl, (3-hydroxyphenyl)methyl, (4-hydroxyphenyl)methyl, (4-methoxyphenyl)methyl, (4-methylphenyl)methyl, (4-fluorophenyl)methyl, (4-fluorophenoxy)methyl, (2,4-dichlorophenoxy)ethyl, (4-chlorophenyl)methyl, (2-chlorophenyl)methyl, (1-phenyl)ethyl, (1-(*p*-chlorophenyl)ethyl, (1-trifluoromethyl)ethyl, (4-methoxyphenyl)ethyl, CH₃OC(O)CH₂-, benzylthiomethyl, 5-(methoxycarbonyl)-*n*-pentyl, 3-(methoxycarbonyl)-*n*-propyl, indan-2-yl, (2-methylbenzofuran-3-yl), methoxymethyl, CH₃CH=CH-, CH₃CH₂CH=CH-, (4-chlorophenyl)C(O)CH₂-, (4-fluorophenyl)C(O)CH₂-, (4-methoxyphenyl)C(O)CH₂-, 4-(fluorophenyl)-NHC(O)CH₂-, 1-phenyl-*n*-butyl, (ϕ)₂CHNHC(O)CH₂CH₂-, (CH₃)₂NC(O)CH₂-, (ϕ)₂CHNHC(O)CH₂CH₂-, methylcarbonylmethyl, (2,4-dimethylphenyl)C(O)CH₂-, 4-methoxyphenyl-C(O)CH₂-, phenyl-C(O)CH₂-, CH₃C(O)N(ϕ)-, ethenyl, methylthiomethyl, (CH₃)₃CNHC(O)CH₂-, 4-fluorophenyl-C(O)CH₂-, diphenylmethyl, phenoxyethyl, 3,4-methylenedioxyphenyl-CH₂-, benzo[*b*]thiophen-3-yl, (CH₃)₃COC(O)NHCH₂-, *trans*-styryl, H₂NC(O)CH₂CH₂-, 2-trifluoromethylphenyl-C(O)CH₂-, ϕ C(O)NHCH(ϕ)CH₂-, mesityl, CH₃C(=NOH)CH₂-, 4-CH₃- ϕ -NHC(O)CH₂CH₂-, ϕ C(O)CH(ϕ)CH₂-, (CH₃)₂CHC(O)NHCH(ϕ)-, CH₃CH₂OCH₂-, CH₃OC(O)CH(CH₃)(CH₂)₃-, 2,2,2-trifluoroethyl,

contol.
B 10
1-(trifluoromethyl)ethyl, 2-CH₃-benzofuran-3-yl, 2-(2,4-dichlorophenoxy)ethyl, ϕ SO₂CH₂-,
3-cyclohexyl-*n*-propyl, CF₃CH₂CH₂CH₂- and N-pyrrolidinyl.

115. (New) The method according to any of Claims 91-93 or 95-97 wherein R² is selected from the group consisting of alkyl, substituted alkyl, alkenyl, cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocycle.

116. (New) The method according to any of Claims 91-93 or 95-97 wherein R² is selected from the group consisting of:

methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, -CH₂CH(CH₂CH₃)₂, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, -CH₂-cyclopropyl, -CH₂-cyclohexyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclohexyl, -CH₂-indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH₃)₂NCH₂CH₂CH₂O-benzyl, *p*-(CH₃)₃COC(O)CH₂O-benzyl, *p*-(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl, *p*-(N-morpholino-CH₂CH₂O)-benzyl, -CH₂CH₂C(O)NH₂, -CH₂-imidazol-4-yl, -CH₂-(3-tetrahydrofuranyl), -CH₂-thiophen-2-yl, -CH₂-(1-methyl)cyclopropyl, -CH₂-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, -CH₂-C(O)O-*t*-butyl, -CH₂-C(CH₃)₃, -CH₂CH(CH₂CH₃)₂, 2-methylcyclopentyl, cyclohex-2-enyl, -CH[CH(CH₃)₂]COOCH₃, -CH₂CH₂N(CH₃)₂, -CH₂C(CH₃)=CH₂, -CH₂CH=CHCH₃ (cis and trans), -CH₂OH, -CH(OH)CH₃, -CH(O-*t*-butyl)CH₃, -CH₂OCH₃, -(CH₂)₄NH-Boc, -(CH₂)₄NH₂, -CH₂-pyridyl, pyridyl, -CH₂-naphthyl, -CH₂-(N-morpholino), *p*-(N-morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl, 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl, 6-methoxynaphth-2-yl, -CH₂CH₂SCH₃, thien-2-yl, and thien-3-yl.

117. (New) The method according to any of Claims 91-93 or 95-97 wherein Z' is -CH₂-.

REMARKS

This application is a divisional of U.S. Application Serial No. 08/996,422 and is directed to methods of use for the compounds of formula I wherein $m=1$ and $n=1$ and pharmaceutical salts thereof. In the parent application restriction was required between the method of using the compounds and the compounds and pharmaceutical compositions. In addition an election of a compound species was required. In the parent application Applicants elected the method of using a species falling within formula I wherein $m=1$ and $n=1$, and $W-C(H)p C=X$ is the caprolactam, dibenzo[b,d]azepin-6-one. Accordingly, the claims of the parent application were limited to the method of use of compounds wherein $n=1$, $m=1$ and $W-C(H)p C=X$ forms certain defined caprolactams. Applicants reserved the right to file divisional applications to all of the subject matter not examined in the parent application. Therefore, the present amendment cancels all of the original claims and presents new Claims 91-117 directed to the methods of use of the compounds of formula I wherein $m=1$ and $n=1$ (defined as formulas IA and IB).

The specification has been amended to provide the cross-reference to the parent application and to correct typographical errors and avoid the use of the same substituent letter having different meanings. Thus where the letters Z and T have been given different meanings in defining a subgenus than given in the generic formula, Z and T have been changed to Z^a and T^a or T^b . Z has been redefined as Z' in the claims deleting the $C(O)$ group from the definition because it now appears in the generic structural formula and omitting the case where T is -O- or -S- and X' or X'' is hydrogen or fluoro. Table 7C (page 597) has also been amended to correct an error in the compound formula for 7C-214 in omitting the alaninyl moiety. Since this compound was prepared via a coupling reaction using an alaninyl-starting material, the product obviously must also contain an alaninyl-group. The specification has also been amended to provide antecedent basis for the cyclic formulas recited in original Claims 17, 19, 21 22, 24-27 and 30-31. These amendments have also been made in the parent application. In addition the specification has been

amended to provide antecedent basis for formula IA, recited in new Claims 91-93 representing the subgenus wherein $m=1$ and $n=1$ and for formula IB in new Claim 95-97, wherein $m=1$ and $n=1$ but grouping the cyclic substituents (Q) recited in original Claims 17, 19, 21, 22 and 24-27.

New Claims 91-112 and 114-116 generally correspond to and are supported by the original method claims defined for the case wherein $m=1$ and $n=1$ and excluding the subject matter examined in the parent application. Support for the new method claims of formula IA, i.e. Claims 91-93, can be found in original Claims 1-3 wherein $m=1$ and $n=1$. Support for new Claim 94 can be found in original Claim 16. Support for the new method claims of formula IB, Claims 95-97, can be found in original Claims 17-31. In addition, the definition of R^2 in Claims 91-97 has been modified to provide antecedent support for the terms 2-aminopyridyl, 2-methylcyclopentyl, cyclohex-2-enyl and $-(CH_2)_4NHC(O)OC(CH_3)_3$ recited in Claim 114; see original Claim 15 and page 17, lines 8-30 of Applicants' specification. In the substituent group $-(CH_2)_4N-Boc$, the term Boc has been replaced by *t*-butyloxycarbonyl (shown above) in accordance with the definition of Boc set forth on page 214 of the specification. Support for the inclusion of pharmaceutically acceptable salts can be found in the definition on page 160, lines 10-17 and original Claim 90. Claims 98-112 are ultimately dependent upon Claims 95-97 and support can be found in original Claims 17-31. Support for new Claim 113 more particularly defining the substituent group R^1 , can be found on page 14, line 28 through page 15, line 23 of the specification. Support for Claim 114 can be found in original Claim 13. In Claim 114, the formula $CH_3C(=NOH)CH_2-$ and the formula for the 1,5-dimethyl-hex-4enyl, correct obvious typographical errors found in original Claim 13 (page 755, line 4 and page 754, line 16 respectively). Further support for the first correction can be found in original Claim 90 and the compound 5-{N'-(4-(hydroxyimino)pentanoyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one. Support for Claims 115 and 116 more particularly defining the substituent group R^2 can be found in original Claims 14 and 15. Lastly, support for Claim 117 more particularly defining Z' can be

found in the definition of Z for example on page 10, lines 18-21 and in the compounds recited on pages 18-86 of the specification, which exemplify the case where Z' is -CH₂-.

Further, unless otherwise defined in the claims, the new claims now expressly recite that the terms aryl, aryloxy, alkaryl, heteroaryl and heterocyclic are optionally substituted to conform with the definitions of these terms in Applicants' specification; i.e. page 156, line 24 - page 157, line 9; page 157, lines 11-12; page 153, lines 27-29; page 158, lines 14-25 and page 158, line 27 - page 159, line 7, respectively.

Examination and allowance are respectfully requested.

In the event the Examiner has any questions concerning the Preliminary Amendment or the Application, the Examiner is requested to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Lawrence S. Squires
Lawrence S. Squires
Registration No. 24,060

P.O. Box 1404
Alexandria, Virginia 22313-1404
(650) 622-2300

Date: July 26, 2001

Attachment A

Marked up version of the Specification

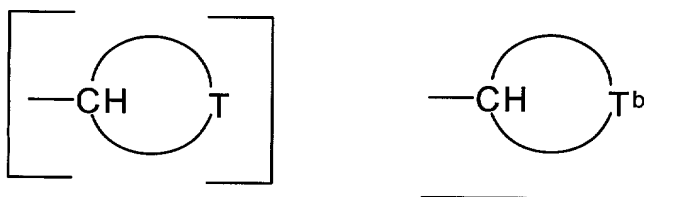
In accordance with the provisions of 35 U.S.C. §1.121(b)(iii), Applicants submit a marked up copy of the amendments made to the specification.

On page 1, paragraph 1 under "Cross reference to Related Applications" replace with the following:

This application [claims the benefit of] is a division of U.S. Application Serial No. 08/996,422 filed December 22, 1997, which claims priority under 35 U.S.C. §119(e) from U.S. Provisional Application No. 60/064,851 which was converted pursuant to 37 C.F.R. §1.53(b)(2)(ii) from U.S. Patent Application No. 08/780,025 filed December 23, 1996.

On page 87 paragraph 1, line 1-21 please replace with the following:

Preferred cyclic groups defined by W and $-\text{C}(\text{H})_p\text{C}(=\text{X})-$ include cycloalkyl, lactone, lactam, benzazepinone, dibenzazepinone and benzodiazepine groups. In one preferred embodiment, the cyclic group defined by W and $-\text{C}(\text{H})_p\text{C}(=\text{X})-$, forms a cycloalkyl group of the formula:

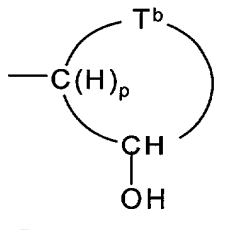
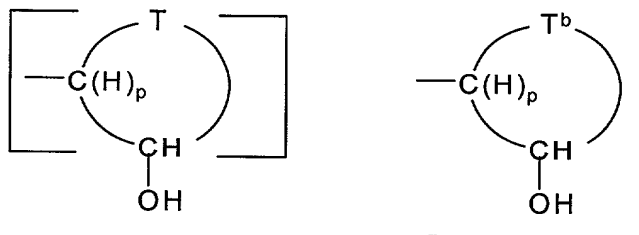


wherein $[\text{T}] \text{ } \underline{\text{T}}^b$ is selected from the group consisting of alkylene and substituted alkylene.

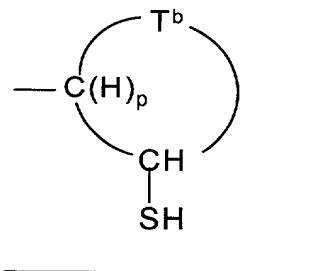
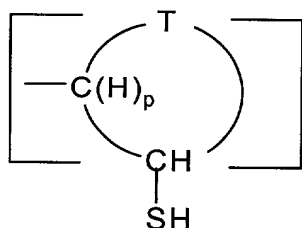
On page 88, second full paragraph starting on line 8 through page 89, line 8 replace with:

In another preferred embodiment, the cyclic group defined by W, together with $-\text{C}(\text{H})_p\text{C}(=\text{X})-$ is a ring of the formula:

Attachment A



or



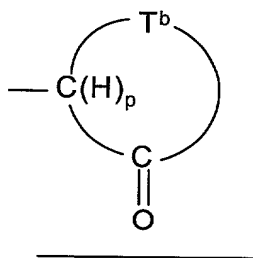
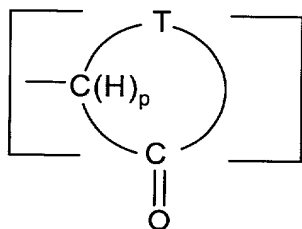
wherein p is zero or one, $[T]$ T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $[-(R^{21}Z)_qR_{21}-$ and $-ZR^{21}-$ where $Z]$ $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of -O-, -S- and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when $[Z]$ Z^a is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and q is an integer of from 1 to 3.

On page 90, second full paragraph starting at line 9 through page 91, line 10 replace with:

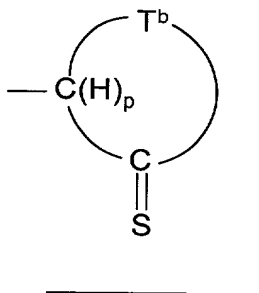
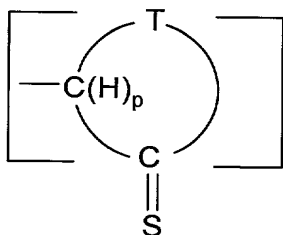
Yet another preferred embodiment of the cyclic group defined by W, together with

Attachment A

$-\text{C}(\text{H})_p\text{C}(=\text{X})-$, is a ring of the formula:



or



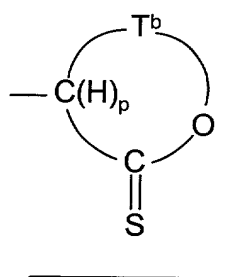
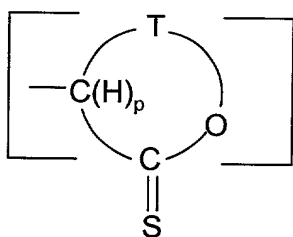
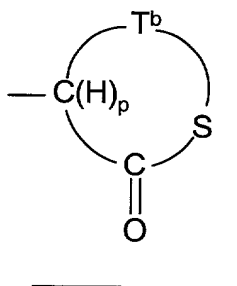
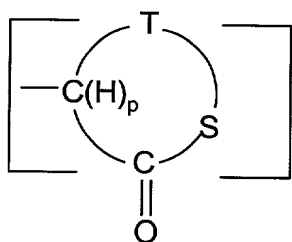
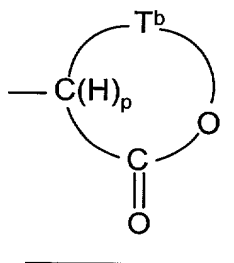
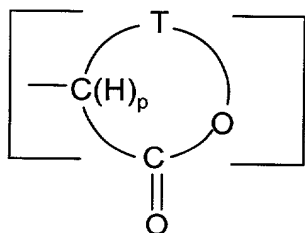
wherein p is zero or one, $[\text{T}] \text{ } \underline{\text{T}}^b$ is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $[-(\text{R}^{21}\text{Z})_q\text{R}_{21}-$ and $-\text{ZR}^{21}-$ where $\text{Z}]$ $-(\text{R}^{21}\text{Z}^a)_q\text{R}^{21}-$ and $-\text{Z}^a\text{R}^{21}-$ where Z^a is a substituent selected from the group consisting of $-\text{O}-$, $-\text{S}-$ and $>\text{NR}^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when $[\text{Z}] \text{ } \underline{\text{Z}}^a$ is $-\text{O}-$ or $-\text{S}-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-\text{O}-$ or $-\text{S}-$, and q is an integer of from 1 to 3.

On page 92, second full paragraph starting at line 7 through page 93, line 37, replace with:

In another preferred embodiment, the cyclic group defined by W, together with

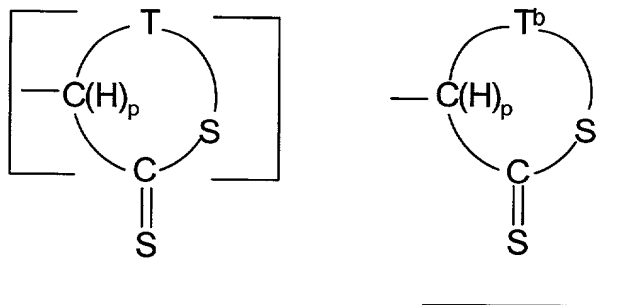
Attachment A

$-\text{C}(\text{H})_p\text{C}(=\text{X})-$, forms a ring of the formula:



or

Attachment A

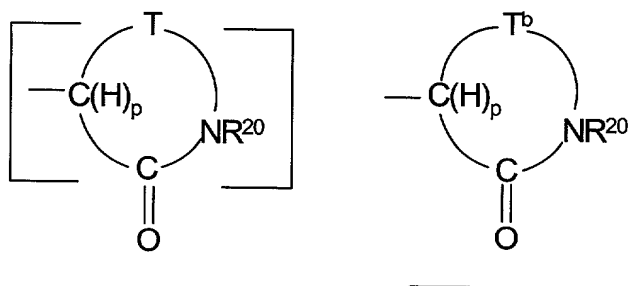


wherein p is zero or one, $[T]$ T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $[-(R^{21}Z)_qR_{21}-$ and $-ZR^{21}-$ where $Z]$ $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of -O-, -S- and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when $[Z]$ Z^a is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and q is an integer of from 1 to 3.

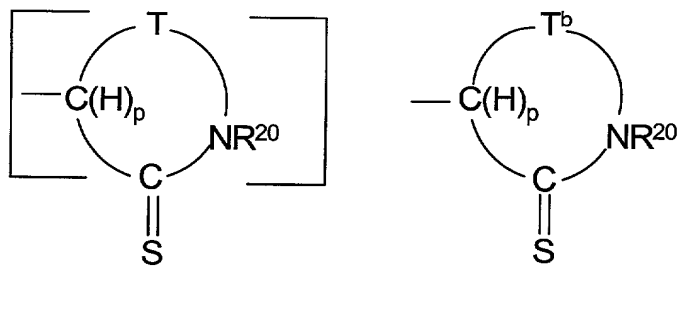
On page 94, second full paragraph, starting on line 20 through page 95, line 30, replace with:

In another preferred embodiment, the cyclic group defined by W and $-C(H)_pC(=X)-$, forms a lactam ring of the formula:

Attachment A



or a thiolactam ring of the formula:

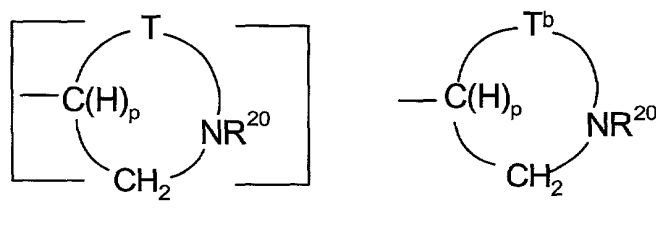


wherein p is zero or one, $[T]$ \underline{T}^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $[-(R^{21}Z)_qR_{21}-$ and $-ZR^{21}-$ where $Z]$ $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of -O-, -S- and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when $[Z]$ \underline{Z}^a is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and q is an integer of from 1 to 3.

Attachment A

On page 99, first paragraph on lines 1-22, replace with:

In another preferred embodiment, the cyclic group defined by W, together with $-(\text{H})_p\text{C}(=\text{X})-$, forms a ring of the formula:

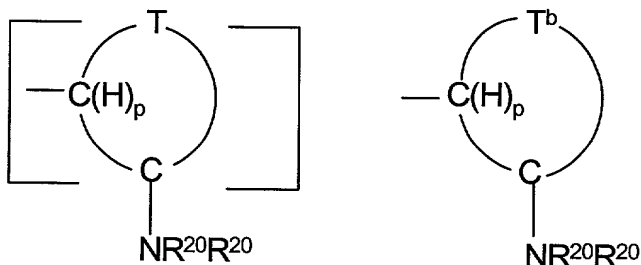


wherein p is zero or one, $[\text{T}] \text{T}^b$ is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $[-(\text{R}^{21}\text{Z})_q\text{R}_{21}-$ and $-\text{ZR}^{21}-$ where $\text{Z}]$ $-(\text{R}^{21}\text{Z}^a)_q\text{R}^{21}-$ and $-\text{Z}^a\text{R}^{21}-$ where Z^a is a substituent selected from the group consisting of -O-, -S- and $>\text{NR}^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when $[\text{Z}] \text{Z}^a$ is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and q is an integer of from 1 to 3.

On page 99, second full paragraph starting at line 24 through page 100, line 10, replace with:

A still further preferred embodiment is directed to a ring group defined by W, together with $-(\text{H})_p\text{C}(=\text{X})-$, of the formula:

Attachment A



wherein p is zero or one, $[T]$ T^b is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $[-(R^{21}Z)_qR_{21}-$ and $-ZR^{21}-$ where $Z]$ $-(R^{21}Z^a)_qR^{21}-$ and $-Z^aR^{21}-$ where Z^a is a substituent selected from the group consisting of -O-, -S- and $>NR^{20}$, each R^{20} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{21} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when $[Z]$ Z^a is -O- or -S-, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the -O- or -S-, and q is an integer of from 1 to 3.

Attachment A

Please replace page 597 of Table 7C with the section of the table below:

Example No.	Compound	Starting Material 1	Starting Material 2	General Procedure	MS
7C-214	5-{N'-(dl-mandelyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one	dl-mandelic acid or dl-alpha-hydroxyphenylacetic acid (Aldrich)	5-(L-alaninyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one	C-P	444.2
7C-215	5-{N'-(p-chloromandelyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one	p-chloromandelic acid (Acros)	5-(L-alaninyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one	C-P	444.2, 478.1
7C-216	5-{N'-(1-alpha-hydroxyisocaproyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one	1-alpha-hydroxyisocaproic acid (Aldrich)	5-(L-alaninyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one	C-P	424.2
7C-217	5-{N'-(4-bromomandelyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one	4-bromomandelic acid (Aldrich)	5-(L-alaninyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one	C-P	522.1, 524.1
7C-218	5-{N'-(1-(+)-lactyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one	1-(+)-lactic acid (Sigma)	5-(L-alaninyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one	C-P	382.2, 454.2
7C-219	5-{N'-(d-3-phenylacetyl)-L-alaninyl}-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one	d-3-phenylacetic acid (Aldrich)	5-(L-alaninyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one	C-P	458.2